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Changing Concepts of the Cause of Diabetes Mellitus

L. J. P. Duncan
B.Sc., M.R.C.P.(Ed.) M.R.C.V.S.
B. F. CLARKE
M.B., M.R.C.P.(Ed.)

Diabetic & Diabetic Department, Royal Infirmary of Edinburgh.

Abstract

Probably the first allusion to diabetes is contained in the papyrus Ebers, dated at about 1500 B.C . and the symptomatology of the disorder was described by Aretaeus in the 1st century A.D. Prior to the late 17th century the causation of diabetes was variously ascribed to excessive food, alcohol, sex or grief or to maladies of the stomach, arteries, blood, nervous and other systems. However, in 1683 the Swiss Brunner recorded that pancreatectomised dogs displayed great thirst and polyuria before dying in coma, and in 1788 Cawley reported destruction of the pancreatic tissue in a patient dying of diabetes. These observations were largely disregarded until further evidence of a possible relationship between diabetes and the pancreas was provided by the classical experiments of von Mering and Minkowski in 1890. Twenty years earlier Langerhans, when aged 20, had described the islets to which his name was given in 1893 by Laguesse who was the first to suggest that they might produce an internal secretion. Schafer in 1895 considered that this secretion might profoundly modify the carbohydrate metabolism of the tissues and the name " insuline" was proposed by de Meyer in 1909.

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CHANGING CONCEPTS OF THE CAUSE OF DIABETES MELLITUS

by

L. J. P. DUNCAN, B.Sc., M.R.C.P.(Ed.) M.R.C.V.S.

and

B. F. CLARKE, M.B., M.R.C.P.(Ed.)

Diabetic & Diabetic Department, Royal Infirmary of Edinburgh.

INTRODUCTION

Probably the first allusion to diabetes is contained in the papyrus Ebers, dated at about 1500 B.C. and the symptomatology of the disorder was described by Aretaeus in the 1st century A.D. Prior to the late 17th century the causation of diabetes was variously ascribed to excessive food, alcohol, sex or grief or to maladies of the stomach, arteries, blood, nervous and other systems. However, in 1683 the Swiss Brunner recorded that pancreatectomised dogs displayed great thirst and polyuria before dying in coma, and in 1788 Cawley reported destruction of the pancreatic tissue in a patient dying of diabetes. These observations were largely disregarded until further evidence of a possible relationship between diabetes and the pancreas was provided by the classical experiments of von Mering and Minkowski in 1890. Twenty years earlier Langerhans, when aged 20, had described the islets to which his name was given in 1893 by Laguesse who was the first to suggest that they might produce an internal secretion. Schafer in 1895 considered that this secretion might profoundly modify the carbohydrate metabolism of the tissues and the name "insuline" was proposed by de Meyer in 1909. About 1900 Opie, in the U.S.A. and Ssobolew in Russia described hyaline changes in or destruction of the islets of Langerhans in diabetics and experimental proof that diabetes was possibly due to defective function of islet cells was provided by McCallum in 1909. He showed that ligation of the pancreatic duct, which caused atrophy of the exocrine pancreatic tissue, was not followed by diabetes but that subsequent destruction of the islet tissue resulted in the appearance of the disorder.

The first suggestion that diabetes in man might be an inherited disorder derives from the observations of Morton in 1696 who noted an extremely high prevalence of the disorder in certain families and this concept was established by von Naunyn in the early years of this century.

Banting and Best in 1921 successfully extracted active insulin from the islet tissue of dogs' pancreas and subsequently demonstrated that it reversed at least the major metabolic changes in experimentally diabetic dogs and in diabetic patients. This seemed in the 1920's to have shown idiopathic diabetes to be due to a simple failure of the beta cells to secrete insulin either because of an inherited functional defect or structural changes in the pancreatic islets.

In the next two decades experimental work in animals demonstrated the influence of other hormones on diabetes. Thus Houssay and his colleagues showed that hypophysectomy ameliorated the diabetes of pancreatectomised

animals, and Long and Lukens found adrenalectomy to have a similar effect. In 1927 Johns et al demonstrated that injection of an extract of the anterior pituitary gland could cause hyperglycaemia and ten years later Young and his associates induced permanent diabetes in dogs by repeated injections of this material; in these diabetic animals beta cell changes occurred and in later years Young attributed this effect to growth hormone contained in the pituitary extract. However, the simplicity and consequent attractiveness of the hypothesis that idiopathic diabetes was due to inadequate insulin secretion was such that this view continued to be held until the mid 1950's. By then, several techniques had been evolved to assay the insulin-like activity of plasma and pancreatic extracts. These led, in the next few years, to remarkable advances in the understanding of insulin metabolism, the factors inducing its release from the pancreas, its effect on the liver, its enzymatic destruction, its distribution throughout the body and the forms in which it is present in the blood. Of particular importance, however, was the demonstration that the plasma of obese diabetics often contained excessive quantities of insulin or insulin-like activity. Furthermore in insulin-dependent diabetics accidentally killed early in the course of the disorder, the islets were not only hypertrophied but sometimes contained normal or increased amounts of extractable insulin. These observations suggested that the primary abnormality of idiopathic or essential diabetes lay outwith the pancreas and was not a simple failure of insulin secretion.

The early view, proposed by Mirsky, that unduly rapid destruction of insulin by insulinase (glutathione insulin transhydrogenase) accounted for the apparent reduction of the hormone's activity in diabetes is no longer tenable; however, the concepts that diminished insulin activity might be due to its abnormal binding to protein in the plasma or the cell membrane or to the presence in the blood of anti-insulin factors or antagonists require further consideration. In addition there is the possibility that diabetes may be a genetically determined abnormality of messenger R.N.A. leading to the production of insulins with altered molecular structure and activity. These possibilities are discussed below along with the glucose-fatty acid cycle of Randle and more recent views concerning the genetics of the disorder. Ref. 1.

HEREDITY

Studies of the prevalence of overt diabetes and impairment of glucose tolerance in the relatives and families of diabetics have unequivocally revealed an inherited predisposition to develop the disorder. Thus, several investigations of twins, one of whom was diabetic, showed that the chances of the other twin having diabetes were about 85% if he was an identical twin and 30% if not identical.

However, the question of the mode or pattern of genetic transmission has only been seriously tackled since the early 1930's. At that time Pincus and White found that the prevalence of diabetes among the offspring of two parents, neither or one or both of whom was diabetic, approximated to a ratio of 1 : 2 : 4, respectively, which suggested that the disorder was inherited as a simple mendelian recessive with a penetrance of about 15-20% (i.e. that only 15-20% of those who were genetically liable to become clinically diabetic did so during their lifetime.)

Although this hypothesis was supported by the studies of Steinberg and Hanhart others have interpreted their own investigations to show either a dominant, a sex-linked, or in the case of juvenile-onset diabetics a recessive and in older-onset diabetics a dominant-type of inheritance. However, as pointed out by Clarke, it is rare for a common disease to be transmitted by a single gene and by postulating incomplete penetrance it is possible to prove almost anything in genetics. In consequence it is not surprising that more recent studies suggest that diabetes is dependent on several genes (i.e. is multifactorial); this might include the dominant transmission of the synalbumin-antagonist as discussed below. Thus, although idiopathic or essential diabetes is undoubtedly a genetically determined disorder much more information is required to establish the mode of its transmission. (Refs. 2. 3. 4. 5.)

GROWTH HORMONE

The possibility that excessive secretion of growth hormone might be causally associated with the appearance of diabetes was based on the following observations: (1) a period of apparently very rapid growth sometimes preceded the appearance of the disorder in young persons, (2) pregnancy occasionally precipitated permanent or temporary diabetes, (3) the

repeated injection of growth hormone — albeit in exceedingly large doses — caused diabetes in dogs and (4) diabetes occurs in acromegalic patients (although in only 20-30% of them). The hypothesis was given further support by the reported finding of increased plasma growth hormone in diabetics; however, the assay method used was unsatisfactory and more recent use of the sensitive and accurate radioimmunoassay has shown no evidence of excess secretion of growth hormone either under basal conditions or in response to secretogenic stimuli in diabetics or pre-diabetics. (Ref. 6, 7).

ANOMALIES OF THE GLUCOSE-FATTY ACID CYCLE

Randle and his colleagues have suggested that one of the earliest, if not the primary, causes of diabetes was a defect of the glucose-fatty acid cycle resulting in the increased release of triglycerides and free fatty acids which reduce both the uptake of glucose by muscle and the effect of insulin on the tissues. This suggestion was based firstly on the fact that fasting, which induces release of these lipids, causes impaired glucose tolerance and relative insulin insensitivity and secondly on observations made on normal subjects and obese mild diabetics fed various types of diets and subjected to a glucose tolerance test. The possibility that the initial excess release of the lipids might be due to increased growth hormone activity was also raised since this hormone has these metabolic effects; more recently a lipolytic hormone derived from the pituitary has been identified and there is some evidence that it may be increased in diabetes. However there are many clinical and experimental observations which cannot be reconciled to this hypothesis. Moreover, among the earliest changes in metabolism that follow upon inadequate insulin activity is fat mobilisation with release of triglycerides and fatty acids; thus these latter changes are likely to be secondary rather than primary in relation to the cause of diabetes. (Ref. 8, 9).

INSULIN ANTAGONISTS

Insulin antibodies, although they may act as insulin antagonists, are found only in patients taking exogenous insulin. However, from evidence obtained in a series of studies dating from 1955, Vallance-Owen and his colleagues have carefully developed a hypothesis that at least one of the fundamental causes of diabetes is the presence in excess of a plasma albumin-bound insulin antagonist. They demonstrated that the albumin fraction of the plasma proteins of non-diabetics inhibited the effect on the rat diaphragm of 1,000 milli units/ml. insulin in vitro; this antagonism was marked when the albumin was present in concentrations of 3.5% or more (i.e. within or above the physiological range) but was lost in concentrations of 1.25% or less. However, the albumin fraction of plasma of patients having diabetes, irrespective of its severity, and of pre- or sub-clinical diabetics was strongly antagonistic at this lower concentration. By various techniques they were able to show that the albumin itself had no inhibitory effect and that the antagonistic property was due to a polypeptide substance associated with but separable from the albumin — this being termed the "synalbumin antagonist". An important finding was that the plasma of patients having "secondary" diabetes due to primary disease (e.g. haemochromatosis) or removal of the pancreas did not contain excess synalbumin. Further studies have shown this synalbumin-antagonist to have many physico-chemical similarities to the B chain of insulin and some support to this suggestion has been provided by the demonstration that albumin — B chain, prepared by incubating B chain with non-antagonistic albumin, is markedly antagonistic to insulin in vitro. However, insulin antagonism has not been demonstrated in vivo following the injection of B chain.

Since it is not unusual for a biochemical reaction to be inhibited by a substance which chemically resembles that which accelerates it, it is not inconceivable that the B chain, released by reductive cleavage of the parent molecule under the influence of insulinase, might antagonise the effect of endogenous insulin and thus bring about diabetes. However, synalbumin is present in the plasma of normal persons so that if this substance is the cause of diabetes then the disorder must result from an exaggeration of a normal phenomenon. Whether or not carbohydrate intolerance or frank diabetes develops and the severity of the diabetes should it occur, will depend on the amount of insulin antagonist present and the degree to which the beta cells can compensate by producing more insulin. It is of considerable interest that even in severe diabetics, hypophysectomy results in the disappearance of the synalbumin antagonist which may explain the considerable fall in insulin requirement and, perhaps, the ameliorating effect of this procedure on certain types of diabetic

retinopathy. It has also been reported that synalbumin positivity occurs much more frequently in the relatives of diabetics than of non-diabetics; if synalbumin positivity is a valid biochemical marker or indicator of the inherited diabetic diathesis then the disorder would seem to be transmitted as a mendelian dominant having a low degree of penetrance.

However, hypotheses related to the B chain albumin-linked antagonist require further proof; and of some importance is the fact that the antagonist does not inhibit the effect of insulin on adipose tissue and there are no studies of its influence on insulin's activity on the liver which is certainly one of the most important organs contributing to the metabolic defects in diabetes. (Refs. 6, 10, 11).

FREE, BOUND AND ABNORMAL INSULINS

Although the subject is still somewhat confused it would appear that insulin is present in the blood in two main physical forms. The first is that in which it is liberated by the beta cells; this is called free or typical insulin. In vitro it is active on both muscle and adipose tissue, and, because this activity is neutralised by insulin — antiserum, it is also called suppressible insulin. In its second form insulin is bound to a protein, is active on fat but not muscle and is not inhibited by antiserum; this form is termed bound, atypical or non-suppressible insulin. Since only free insulin is detectable in the pancreatic vein whereas both occur peripherally, it is suggested that binding occurs in the liver. In non-diabetics the ratio of free to bound insulin in the plasma varies according to the metabolic state and needs of the body; for example in fasting most of the insulin is present in bound form and after meals in free form. Several authorities, in particular Antoniades, have postulated that diabetes may be due to excessive insulin binding or an inability to convert bound into free insulin. Certainly the plasma of obese persons with mild diabetes contains an excessive proportion of bound insulin even after the administration of glucose. Since the albumin-bound insulin antagonist, discussed above, does not inhibit insulin activity on fat this factor may be associated with the difference in metabolic activity between free and bound insulin. Recent work by Cahill and his colleagues, however, suggests that in vivo only free insulin can pass into the extra-vascular fluids and thus be able to come into contact with and influence the metabolism of peripheral tissue cells; thus an absolute reduction of free insulin, brought about by excessive binding of the remainder may be causally related to the metabolic disturbance.

Insulinase, not only promotes the reductive cleavage of the disulphide bonds of insulin to release its A and B chains but can also bring about their reconjugation. The possibility has been raised that a genetic defect of this enzyme's activity might promote abnormal re-conjugation of the A and B chains resulting in new forms of insulin having either no activity or possessing antigenic properties. However, to date no consistent abnormality in the chemical structure of insulin in human diabetes has been detected. (Refs. 12, 13, 14, 15.)

ROLE OF THE PANCREAS

The elucidation of the chemical and molecular structure of insulin by Sanger raised the possibility that diabetes might be due to the production of abnormal insulins; the protein synthesis of insulin is under the influence of messenger R.N.A., the form of which is genetically determined. However, there is as yet no evidence to support such a hypothesis.

Although the initial cause or causes of the metabolic abnormalities in diabetes is not a primary reduction in insulin secretion but rather a failure to produce enough extra insulin to overcome factors, of extra pancreatic origin, which diminish its effective activity, it must be remembered that secondary exhaustion of the beta cells can occur with decreasing capacity and eventual inability to produce insulin. This explains why diabetes controlled by diet alone may, after some years, require treatment with a sulphonylurea (which uncouples insulin from inactive protein-bound complexes), why secondary-sulphonylurea failure occurs and the efficacy of the diguanides (which potentiate the effect of insulin on the tissues) in such patients, and, of course, the development of ketoacidosis when insulin therapy is discontinued in insulin-dependent diabetics. Thus although the primary cause of diabetes lies outwith the pancreas, the metabolic severity of the established disease depends very largely on the capacity of the beta cells to respond to the challenge; like a tired horse they may be flogged to death.

Finally it is necessary to consider obesity, pregnancy, stress and injury which are sometimes listed as causes of diabetes. They are

not causes of the disorder but may precipitate its overt clinical manifestations in those who are genetically pre-disposed to diabetes. (Ref. 16.)

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For the sake of simplicity and because a complete bibliography would be too long the references given at the end of each section are limited to the more recent papers and works relevant to the subject matter therein considered.

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DIAGNOSTIC PROBLEM

Subject :

J.W., Male, Age 28; Rubber works employee.

Presenting Complaint :

Abdominal colic and constipation.

History of Complaint :

Over the past six months J.W. has suffered from attacks of abdominal colic. These have been increasing in frequency and severity; they now occur about twice per week, and are not in any way related to time of day or to food of any type. The pain is unrelieved by food, alkali or warmth. During an attack the pain is central abdominal of a colic type, and may last for up to two hours.

He has also complained of anorexia over the past two months; and generalised weakness, especially in the grip of his hands, has become evident.

Past history :

Usual childhood illnesses.

Social history :

Not relevant.

Family history :

No history of any familial diseases.

Examination :

No obvious jaundice or cyanosis. Marked pallor of mucous membranes and a pale complexion.

C.V.S. — Pulse 84. Regular in time and force. Apex beat in 5th interspace, within M.C.L. Heart sounds I and II. No murmurs.

R.S. — No abnormality detected.

G.I.S. — Tongue and fauces clean.
Dark line around gum margins.
Abdomen moves with respiration. No visible veins, peristalsis or masses.
No guarding. No tenderness either direct or rebound.
No masses palpable. Liver not enlarged.
Spleen and kidneys not palpable.

C.N.S. — No loss of function detected in cranial nerves.
No sensory peripheral loss.
Slight bilateral weakness of hand grip.
No obvious muscle wasting.

Findings :

1. History of abdominal colic, constipation, anorexia and weakness.
2. Pallor of mucous membranes.
3. Darkening of gum margins.
4. Weakness of grip.

What is the diagnosis? How would you confirm it? How would you treat it?

See page 56.